DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 August 2011 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 26 August 2011 has been entered in full. Claims 1-3, 5, 7, 8, 11, 14, 15, 18, 23, 24, 26, 30, and 32-35 are amended. Claims 29 and 31 are cancelled.

Claims 1-28, 30, and 32-35 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to claims 1, 5, 23, and 33 as set forth at pages 3-4 of the previous Office Action (30 March 2011) are *withdrawn* in view of the amended claims (26 August 2011).

2. The rejections of claims 1-5, 7-28, 30, 32, 33, and 34 under 35 U.S.C. 112, second paragraph, as set forth at pages 4-5 of the previous Office Action (30 March 2011) are *withdrawn* in view of the amended claims (26 August 2011).

3. The rejection of claim 35 under 35 U.S.C. §101 as set forth at pages 5-6 of the previous Office Action (30 March 2011) is *withdrawn* in view of the amended claim (26 August 2011).

4. The rejection of claims 18-21 and 30 under 35 U.S.C. 112, first paragraph (scope of enablement) as set forth at pages 6-11 of the previous Office Action of 30 March 2011 is *withdrawn* in view of the amended claims of 26 August 2011, which no longer read upon gene therapy.

5. The rejection of claims 7 and 8 under 35 U.S.C. §102(b) as being anticipated by Queen et al. (U.S. Patent 5,530,101) as set forth at pages 11-12 of the previous Office Action (30 Mach 2011) is *withdrawn* in view of amended claim 7 (26 August 2011).

New Claim Objections

6. Claims 1, 19, and 23 are objected to because of the following informalities:

6a. In claim 1, line 9, a space should be inserted between "SEQ ID NO: 6)" and "and".

6b. In claim 19, line 2, the term "contains" should be amended to recite "comprises".

6c. In claim 23, the phrase "antibody of claim 1 or a fragment thereof and a pharmaceutically acceptable carrier" is lengthy and slightly unclear as to whether the antibody and carrier are administered together. Claim 23 could be clarified and shortened by amending the claim to depend from claim 18 (a composition comprising the antibody and a carrier). For example, claim 23, could be amended to recite, "comprising administering the composition of claim 18 to said mammal...".

New Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 24-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 24-28 are rejected as being indefinite because a broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 24 recites the broad recitation "mammal", and the claim also recites "preferably a human" which is the narrower statement of the range/limitation. It is unclear whether the limitation following the phrase "mammal" is part of the claimed invention. See MPEP § 2173.05(d).

Maintained Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 23-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preventing or treating TLR2-induced septic shock in a mammal comprising administering to said mammal the isolated cross-reactive antibody, ***does not reasonably provide enablement for*** a method of preventing or treating TLR2 mediated inflammation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pages 6-11 of the previous Office Action of 30 March 2011 and at page 14-16 of the Office Action of 29 April 2010.

Claim 23 is directed to a method of preventing or treating TLR2-mediated inflammation in a mammal comprising administering the antibody of claim 1 and a pharmaceutically acceptable carrier to said mammal in an effective amount to prevent or treat said TL2-mediated inflammation.

At page 10 of the Response of 26 August 2011, Applicant argues that the specification is enabling for a method of preventing or treating TLR-2 mediated-inflammation in a mammal comprising administering the TLR2 cross-reactive antibody to the mammal as the specification teaches the use of TLR2 cross-reactive antibodies to inhibit mediators of inflammation (page 16, lines 11-13; Figures 3c, 3d, 5a, 11, and 12). Applicant states that the examples further show that T2.5 inhibited a TLR2 mediated increase in the transcription factor NF-kappa B and that subcellular NF-kappa B translocation was blocked upon TLR2 specific challenge of primary human macrophages (page 26, lines 29-30). Applicant continues to assert that the examples show that T2.5 inhibited a TLR2 mediated increase in the pro-inflammatory cytokine IL-8 (page

24, line 31 to page 25, line 3) and inhibited a TLR2 mediated increase in IL-6 and IL-12p40 (Figures 5c, 5d). Applicant contends that the specification is enabling for a method of preventing or treating TLR-2 mediated inflammation in a mammal comprising administering the TLR2 cross-reactive antibody to the mammal.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that the anti-TLR2 antibody, T2.5, lowers mouse serum levels of TNFα, IL-8, IL-6, and IL-12p40 as compared to control when the mice are challenged with P_3CSK_4 and D-galactosamine (page 26, bottom of page 25 through page 26, lines 1-3). The specification discloses that in mice given T2.5 either prior (1h) or up to 2 h after or *B. subtilis* microbial challenge, all *B. subtilis* challenged mice survived (page 26, bottom of 1st full paragraph; Figure 6b). The specification teaches that treatment of T2.5 3 h after potentially lethal injection saved 75% of the mice challenged (page 26, bottom of 1st full paragraph; Figure 6b). However, the specification does not teach any methods or working examples that indicate that TLR2 cross-reactive antibodies prevent or treat TLR2-mediated inflammation, other than TLR2-mediated septic shock. The claims have been broadly interpreted by the Examiner as reading upon the treatment or prevention of a plethora of inflammatory conditions. However, the limited teachings of the specification regarding prevention and treatment of septic shock, are not adequate guidance, but are merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat or prevent all TLR2-mediated inflammation. The skilled artisan must resort to trial and error experimentation to determine the optimal agent, as well as the optimal dosage, duration, and mode of administration that results in the prevention and treatment of TLR2-mediated

inflammation. Such trial and error experimentation is considered undue. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed."

Furthermore, as discussed in the previous Office Action, the relevant literature teaches that the role of TLR2 in many diseases or conditions is not certain or predictable. For example, McCormack et al. disclose that elevated levels of TLR2 have been found in macrophages isolated from rheumatoid arthritis synovium (Arthritis Res Therapy 11(5): 243, 2009;; page 244, column 2, 2nd paragraph). McCormack et al. also disclose that IL1rn-/-TLR2-/- animals develop severe arthritis, suggesting an anti-inflammatory role for TLR2 in that model (page 244, column 2, 3rd full paragraph). McCormack et al. state that the anti-inflammatory nature of TLR2 in the IL1-receptor antagonist knockout model is in contrast to results obtained in a streptococcal cell wall induced model of arthritis, where mice deficient for TLR2 have reduced severity of arthritis (page 244, column 2, 3rd full paragraph). Cario, E. also teaches that deficient TLR2 signaling may imbalance commensal-dependent intestinal epithelial barrier defense, facilitating mucosal injury and leading to increased susceptibility to colitis (Mucosal Immunol 1(Suppl 1): S62-S66, 2008; abstract). Specifically, Cario discloses that loss of TLR2 leads to exacerbation of intestinal inflammation in DSS colitis with high morbidity and mortality (page S64, bottom of column 1 through column 2). Cario indicates that treatment with a synthetic TLR2 ligand significantly suppresses mucosal inflammation *in vivo* (page S64, column 2, last paragraph). Hence, in view of the lack of guidance in the instant specification and the contradictory state of the art, there is no clear nexus or mechanism between TLR2 and TLR2-mediated inflammatory processes, other than TLR2-induced septic shock. A large quantity of experimentation would be

required of the skilled artisan to identify the nexus between TLR2 and all TLR2-mediated inflammation (and inflammatory conditions) and administer the claimed TLR2 cross-reactive antibodies for prevention or treatment. Such experimentation is considered undue. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily prevent or treat TLR2-mediated inflammation in a mammal by administering cross-reactive TLR2 antibodies.

Due to the large quantity of experimentation to treat and prevent TLR2-mediated inflammation; the lack of direction/guidance presented in the specification regarding the same; the absence of working examples directed to the same; the complex nature of the invention; and the breadth of the claims, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Conclusion

Claims 1, 19, 23, and 30 are objected. Claims 23-28 are rejected. Claims 2-18, 20-22, 32-35 are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571)272-0881. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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